UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,402	09/17/2001	Julio Cesar Aguilar Rubido	976-11 PCT/US	3056

7590 12/04/2001

Ronald J Baron
Hoffmann & Baron
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
FOLEY, SHANON A	
ART UNIT	PAPER NUMBER
1648	7

DATE MAILED: 12/04/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/857,402	Applicant(s) AGUILAR RUBIDO ET AL.	
	Examiner Shanon A. Foley	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 September 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant cancelled claims 1-10 in paper no. 5 and added new claims 11-23.

Drawings

Figure 5 of the drawings is objected to because the language within the drawing is in Spanish. Correction is required accompanied by an assurance that no new matter is introduced.

Claim Objections

Claim 21 is objected to for failing to further limit claim 11. Claim 11 states the vaccine composition is for nasal administration, which is a mucosal membrane, recited in claim 21. Claims 22 and 23 also fail to further limit independent claim 11 because a vaccine by definition is administered to prevent, ameliorate, or treat infectious diseases, see Dorland's Illustrated Medical Dictionary, 28 edition. Philadelphia, WB Sauders, 1994, page 1787.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites "...antigen synergizing in adjuvant effect...". It cannot be determined what is intended by this phrase. Does administration of the vaccine and surface antigens have a synergistic effect on the immune response in general? Or, is the immune response augmented specifically to both antigens? Or, is the immune response specifically enhanced to the surface antigen when the vaccine antigen is administered in conjunction with the surface antigen? Also,

since the claim differentiates the surface and the *vaccine* antigen (emphasis added), does applicant intend for the vaccine formulation to be prophylactic only against the virus supplying the vaccine antigen and not the surface antigen?

Claims 16-18 are vague and indefinite because the claims 16-18 state that the a virus-like particle (VLP) comprise nucleocapsid antigens from hepatitis B (HBV), hepatitis C (HCV), or papillomavirus (HPV) nucleocapsid antigens. Claim 15 specifies that the viral antigen is a viral nucleocapsid. Does applicant intend for a viral nucleocapsid protein to be incorporated into a VLP? Or, are the VLPs hybrid molecules in which two distinct nucleocapsid proteins are fused together? The specification teaches on page 5, line 28, that the "HBsAg is mixed with HBcAg", page 6, line 3 states that "HBsAg is mixed with other antigens", and page 7, line 19, defines adjuvation as a mixing process. The act mixing antigens denotes that the antigens are placed within the same proximity, such as a test tube, and not necessarily fused into one unit. If applicant intends for the antigens to be fused or incorporated into another nucleocapsid, and not mixed together, the claim language does not reflect this limitation.

Claim 19 is vague because it cannot be discerned how an antigen is immuno-enhanced by another antigen. Does applicant intend for both antigens to have a synergistic effect on the immune system when administered together, or is the immune response more specific to the vaccine antigen if it is co-administered with HBsAg?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to various virus-like particles containing nucleocapsid antigens from hepatitis B, hepatitis C, or papillomavirus nucleocapsid antigens. As discussed previously, it cannot be discerned whether applicant intends for these antigens to be mixed or fused. The scope of the claims encompasses any mixture or fusion of any HBsAg and any viral nucleocapsid. There is no support in the disclosure teaching how the skilled artisan could fuse any viral nucleocapsid to HBsAg. There is also no support found for HCV, HBV, or HPV VLPs incorporating HBsAg. The specification only teaches "mixing" two antigens together; see page 5, line 28, page 6, line 3, and page 7, line 19. The specification does not teach how the skilled artisan could identify a mixture, fusion, or complex of HBsAg and any viral nucleocapsid that would satisfy the intended vaccine function. The specification also does not teach possession of these complexes, fusions, or mixtures, nor does the specification teach how the skilled artisan could make the hybrid formulations.

Claims 15-19 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are dawn to a vaccine formulation comprising a hepatitis B surface antigen (HBsAg) and any viral nucleocapsid. The nucleocapsid is a virus-like particle (VLP) from

hepatitis B or hepatitis C, or Human Papillomavirus (HPV), or any virus (claims 15-18). The vaccine also can be made of HBsAg and any other antigen, not limited to viral antigens (claim 19). It cannot be determined whether the claimed are directed to treating and preventing both hepatitis B and the infectious disease the second antigen is derived from, such as HPV and HCV, or just hepatitis B. It also cannot be determined from the claim language whether HBsAg is encapsulated within the various VLPs, or if the VLP and HBsAg are forming a chimeric molecule, or whether it is intended that the VLPs and HBsAg are co-administered in the same mixture. There is no teaching in the specification that would enable the skilled artisan a way to make HBsAg encapsulated within the various VLPs or making a chimeric molecule comprising the VLP and HBsAg. The specification only teaches "mixing" two antigens together; see page 5, line 28, page 6, line 3, and page 7, line 19. Also, the examples on pages 7-11 teach co-administering the various antigens.

The specification does not teach how the skilled artisan could identify a mixture, fusion, or complex of HBsAg and any viral nucleocapsid that would satisfy the intended vaccine function. The working examples are limited to administering various antigen combinations to mice and monitoring antibody response. The skilled artisan would have no way to predict how long the elevated antibody responses lasted after administration of the vaccine from the data in the working examples.

There is no data in the examples that would indicate to the skilled artisan that mice developed an immune response sufficient to block infection from HBV, HCV, HPV, or any other virus. The mice were not challenged with any virus after administration of the vaccine. In addition, there is no animal model presented that would indicate that infection of hepatitis,

papillomavirus, or any other virus could be treated by the vaccine composition. Lanford et al. (ILAR Journal. 2001; 42 (2): 117-26, abstract only), teaches that the only acceptable animal model currently available for study of HCV infections is the chimpanzee. Since the working examples are limited to experiments in mice, the skilled worker would not accept that an increase in antibody response in mice to hepatitis antigens would sufficiently indicate that the instant vaccine composition has ameliorative or prophylactic properties with respect to HCV. Coursaget et al. (Cancer Surveys. 1998; 33: 355-381, abstract only), teaches that although some success has been observed in mouse models of papillomavirus infection, animal models more relevant to humans, have demonstrated only poor results. Farrell (Drugs. 2000; 60 (4): 701-710), teaches challenges that still exist in developing HBV therapeutics for long-term efficacy, such as antiviral resistance mutations in HBV reverse transcriptase, see the abstract. Farrell also teaches that the attack on Hepatitis core-presenting hepatocytes by cyctotoxic T cells (CTL) results in hepatic inflammation and necrosis of the liver, see the first paragraph on page 702. There is no discussion or working example directed to monitoring the CTL response with respect to hepatitis infection or addressing concerns in the art in regard to antiviral resistance mutations. The skilled artisan could not predict how a subject would respond to the vaccine composition, or whether the vaccine would have any efficacy for treating infection or preventing it.

Therefore, due to the ambiguity of the claims, the scope of the claims which encompass treating and preventing any infection with the vaccine composition, the lack of guidance provided by the inventor for making encapsulated HBsAg or chimeric molecules, the lack of ability the skilled artisan would have in making these products, the lack of guidance provided by the inventor with regard to CTL responses or how long the antibody response lasted, the lack of

working examples with an appropriate animal model, the lack of data in the working examples demonstrating preventative capabilities of the vaccine upon challenge and treatment capabilities of the vaccine when administered during infection, the lack of predictability in the vaccine art, and the undeveloped state of the art, it is determined that an undue amount of experimentation would be required of the skilled artisan to make or use the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 11-13, 20, 21, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Chatfield (US 6,048,536).

The claims are drawn to a vaccine composition for nasal administration comprising a surface antigen from a virus and another antigen that is administered by spray.

Chatfield teaches a pharmaceutical product comprising influenza virus antigens haemagglutinin and neuraminidase, which is administered intranasally by aerosol, see claims 1, 2, 5, 6, 9-11, 14-16, and 19. The vaccine formulation is also formulated as liquids or dry powders and includes preservatives and stabilizers, see column 3, lines 9-16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chatfield (US 6,048,536), in further view of Fields et al. (Virology, Vol. 1, 3rd edition, Philadelphia, Lippencott, Williams, and Wilkins, publishers. 1996: page 1356).

The claim is drawn to a vaccine formulation further comprising a second vaccine antigen. See the teachings of Chatfield above. Chatfield does note teach administering another antigen in addition to haemagglutinin and neuraminidase. However, one of ordinary skill in the art at the time the invention was made would have been motivated incorporate another influenza antigen, such as M_2 (see figure 1 on page 1356 of Fields et al.), into the vaccine composition taught by Chatfield to specifically stimulate the immune response against more viral antigens presented on the surface of the virion. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SAF
Shanon Foley/SAF
November 29, 2001

James C. Housel
JAMES HOUSEL 12/3/01
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600